PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference BET03P0927	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IB 03/04513	International filing date *(day/month/year)* 14.10.2003	Priority date *(day/month/year)* 15.10.2002

International Patent Classification (IPC) or both national classification and IPC
C12Q1/68

Applicant
INSTITUT NATIONAL DE LA SANTE ET DE LA ...

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
10.03.2004	23.11.2004
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Gabriels, J Telephone No. +31 70 340-4282

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB 03/04513

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-24 as originally filed

Claims, Numbers

1-11 as originally filed

Drawings, Sheets

1/2-2/2 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☒ contained in the international application in written form.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-9
	No:	Claims	10,11
Inventive step (IS)	Yes:	Claims	1-9
	No:	Claims	10,11
Industrial applicability (IA)	Yes:	Claims	1-11
	No:	Claims	

2. Citations and explanations

   see separate sheet

V. Reasoned statement (Continuation)

2.1 CITATIONS

Reference is made to the following documents:

D1: WO 02 36631 A (KAMOHARA MASAZUMI ;MATSUMOTO MITSUYUKI (JP); SAITO TETSU (JP); OHI) 10 May 2002 (2002-05-10)

D2: DATABASE EBI [Online] EMBL; Homo sapiens 3 BAC RP11-25K24, 6 March 2000 (2000-03-06) MUZNY DM ET AL: retrieved from EBI, accession no. EM_HUM:AC024886 Database accession no. AC024886 XP002242768

D3: WO 01 046454 A (COR THERAPEUTICS INC) 28 June 2001 (2001-06-28)

D4 HUMENY ANDREAS ET AL: 'Genotyping of thrombotic risk factors by MALDI-TOF mass spectrometry' CLINICAL BIOCHEMISTRY, vol. 34, no. 7, October 2001 (2001-10), pages 531-536, XP002229944 ISSN: 0009-9120

D5 CONLEY PAMELA ET AL:' Unique mutations in the P2Y12 locus of patients with previously described defects in ADP-dependent aggregation", BLOOD, 43rd Annual Meeting of the American Society of Hematology, Part 2, December 07-11, 2001, November 16, 2001, vol 98, no. 11 Part 2, page 43b, ISSN: 0006-4971

D6: MUKHERJEE DEBABRATA ET AL: 'Pharmacogenomics in cardiovascular diseases' PROGRESS IN CARDIOVASCULAR DISEASES, vol. 44, no. 6, May 2002 (2002-05), pages 479-498, XP008025596 ISSN: 0033-0620

D4 and D6 are cited from the examiner's own knowledge. A copy of these documents is annexed to this communication.

2.2 NOVELTY (Art. 33(2) PCT)

2.2.1 The simultaneous presence of the polymorphisms at positions 139 (T), 745 (C), and 801(A) of the intron (SEQ ID NO:1), and at position 52 (T) of exon 2 (SEQ ID NO:2) of the P2Y12 receptor gene (haplotype H2) is indicative of a higher risk for developing thrombosis or peripheral arterial disease. The link between this haplotype and a higher risk for developing thrombosis or peripheral arterial disease is not known from the prior art D1-D6. In view of the prior art cited, claims 1-9

appear to be novel and meet therefore the requirements of Art. 54 EPC.

2.2.2 D1 discloses the use of PCR primers ABL59206 and ABL59207 to amplify a DNA sequence encoding a human P2Y12 protein (cf example 1: P2TAC). These primers are suitable for amplifying the part of the P2Y12 gene sequence containing position 52 of exon 2 (SEQ ID No 2). These primers therefore fall within the scope of claim 11. In view of D1, claim 11 is not novel.

2.2.3 D2 discloses an isolated nucleic acid (AC024886) encoding the P2Y12 receptor and comprising all the polymorphisms of claim 10. D2 therefore falls within the scope of claim 10. In view of D2, claim 10 is not novel.

2.3 D3 discloses the use of PCR primers to amplify a cDNA sequence encoding a human P2Y12 (here called P2TAC) protein (cf figure 5). These primers are suitable for amplifying the part of the P2Y12 gene sequence containing position 52 of exon 2 (SEQ ID No 2). These primers therefore fall within the scope of claim 11. In view of D3, claim 11 is not novel.

2.3.1 The present application does not satisfy the criterion set forth in Article 33(2) PCT because the subject-matter of claims 10 and 11 is not new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT).

2.4 INVENTIVE STEP (Art. 33(3) PCT)

2.4.1 Document D4 is considered to represent the most relevant state of the art for independent claims 1 and 6 and discloses methods for determining a risk for developing thrombosis by determining the genotype of thrombotic risk factor genes. Individual risk of thrombotic disease is highly associated with allelic sequence variations in the blood clotting factor V (F5) and factor II (F2) genes (cf. page 531). The subject-matter of independent claims 1 and 6 differs from D4 in that the simultaneous presence of the polymorphisms at positions 139 (T), 745 (C), and 801(A) of the intron (SEQ ID NO:1), and at position 52 (T) of exon 2 (SEQ ID NO:2) of the P2Y12 receptor gene (haplotype H2) is indicative of a higher risk for developing thrombosis or peripheral arterial disease.

2.4.2 The problem to be solved by the present invention may therefore be regarded as providing alternative gene polymorphisms indicative of a higher risk for developing thrombosis or peripheral arterial disease. The proposed solution is the

determination of the presence of the H2 haplotype of the P2Y12 receptor gene.

2.4.3 Unique mutations in the P2Y12 locus of patients with previously described defects in ADP-dependent aggregation are known from D5. However, the involvement of the H2 haplotype of the P2Y12 receptor gene in thrombosis or peripheral arterial disease is not known nor hinted to in D5 taken either alone or in combination with D4. The use the H2 haplotype to solve the problem of independent claims 1 and 6 would therefore not be obvious.

2.4.4 The subject-matter of dependent claims 2, 3, 7-9 depends on independent claims 1 and 6 and is therefore considered to satisfy the criterion set forth in Article 33(3) PCT.

2.4.5 In view of the above, the subject-matter of claims 1-3, 6-9 meets the requirements of Article 33(3) PCT, because the subject-matter of claims 1-3, 6-9 involves an inventive step (Rule 65(1)(2) PCT).

2.4.6 Document D6 is considered to represent the most relevant state of the art for independent claim 4 and discloses methods for determining the sensitivity of a subject to treatments for cardiovascular diseases. The subject-matter of independent claim 4 differs from D6 in that the simultaneous presence of the polymorphisms at positions 139 (T), 745 (C), and 801(A) of the intron (SEQ ID NO:1), and at position 52 (T) of exon 2 (SEQ ID NO:2) of the P2Y12 receptor gene (haplotype H2) is indicative of a lower sensitivity for thienopyridine therapy.

2.4.7 The problem to be solved by the present invention may therefore be regarded as providing alternative gene polymorphisms indicative of a lower sensitivity for thienopyridine therapy. The proposed solution is the determination of the presence of the H2 haplotype of the P2Y12 receptor gene.

2.4.8 Unique mutations in the P2Y12 locus of patients with previously described defects in ADP-dependent aggregation are known from D5. However, the involvement of the H2 haplotype of the P2Y12 receptor gene in a lower sensitivity for thienopyridine therapy is not known nor hinted to in D5 taken either alone or in combination with D6. The use the H2 haplotype to solve the problem of independent claim 4 would therefore not be obvious.

2.4.9 Claim 5 depends on independent claim 4 and is therefore considered to satisfy the

criterion set forth in Article 33(3) PCT.

2.4.10 In view of the above, the subject-matter of claims 4 and 5 meets the requirements of Article 33(3) PCT, because their subject-matter involves an inventive step (Rule 65(1)(2) PCT).

2.4.11 In view of the above, the present application does not meet the requirements of Article 33(3) PCT, because the subject-matter of claims 10 and 11 does not involve an inventive step (Rule 65(1)(2) PCT).

2.5 MISCELLANEOUS

2.5.1 Although claims 1 and 6 have been drafted as separate independent claims, they appear to relate effectively to the same subject-matter and to differ from each other only with regard to the terminology used for the features of that subject-matter. The aforementioned claims therefore lack conciseness. Moreover, lack of clarity of the claims as a whole arises, since the plurality of independent claims makes it difficult, to determine the matter for which protection is sought, and places an undue burden on others seeking to establish the extent of the protection. Hence, claims 1 and 6 do not meet the requirements of Article 6 PCT.